



Treatment outcomes for multidrug-resistant tuberculosis in Eastern Taiwan

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ABSTRACT

Objectives: The objective of this study is to evaluate the treatment outcomes of patients with multidrug-resistant tuberculosis (MDR-TB) under special programmatic management in Eastern Taiwan over the past 10 years. **Materials and Methods:** All newly diagnosed MDR-TB patients and MDR-TB patients enrolled previously with persistent positive cultures were included in this study, from May 2007 to April 2017, in Eastern Taiwan. A panel of pulmonologists designed the initial MDR-TB regimens. Subsequently, regimens were adjusted according to drug susceptibility test results for second-line drugs. Mobile teams were organized for treatment support, and several measures were adapted to safeguard effective treatment support. **Results:** A total of 178 patients with bacteriological confirmed pulmonary MDR-TB were identified, of whom 167 had treatment outcomes when the study was conducted. Of these 167 patients, 120 (71.9%) were cured, 11 (6.5%) completed therapy (78.4% had successful treatment), 25 (15.0%) died, 9 (5.4%) had treatment failure, none were transferred out, and 2 (1.2%) were lost to follow-up. Surgery was performed on 8 (4.8%). **Conclusions:** This is an analysis of the treatment outcomes after adopting the Directly Observed Treatment, Short-course Plus program to treat MDR-TB patients in Eastern Taiwan. We had a low proportion of loss-to-follow-up, resulting in a high treatment success rate. This program serves as an effective model in providing quality care to patients with MDR-TB.

KEYWORDS: Directly observed treatment, Short-course Plus program, Eastern Taiwan, Multidrug-resistant tuberculosis, Treatment outcomes

INTRODUCTION

One hundred and thirty-five years since the identification of *Mycobacterium tuberculosis* by Robert Koch in 1882 and 72 years after the introduction of streptomycin (SM) by Selman Waksman in 1945, tuberculosis (TB) remains an important public health concern worldwide. The World Health Organization (WHO) estimated that 3.9% of new TB cases and 21% of previously treated cases were multidrug-resistant TB (MDR-TB) or rifampicin (RMP)-resistant TB (RR-TB). An estimated 580,000 new cases of MDR/RR-TB occurred in 2015, resulting in 250,000 deaths. MDR-TB has become a serious challenge for global TB control. Globally, the MDR-TB treatment success rate was 52% in 2013 [1]. Diagnosis of MDR-TB requires quality-assured drug susceptibility testing (DST), and treatment requires prolonged administration of costly and toxic second-line anti-TB drugs, which are commonly far beyond the management capacity in resource-limited settings [2].

In the 1990s, the WHO recommended the Directly Observed Treatment, Short-course (DOTS) strategy for TB control. Building on the model of DOTS, the WHO established a working group on a new strategy for the treatment of MDR-TB, termed “DOTS-Plus” in 1999 [3]. The Taiwan MDR-TB Consortium (TMTC) implemented the programmatic management of drug-resistant TB in May 2007. The TMTC consists of five management groups. Hualien Tzu Chi Hospital is the lead hospital in Eastern Taiwan and works in cooperation with other regional hospitals. In this paper, we report the outcomes of MDR-TB patients in Eastern Taiwan.

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MATERIALS AND METHODS

Study setting

Taiwan is a high-income country with a per capita gross domestic product of US \$ 22,287 in 2015. The incidence of TB was 45.7 per 100,000 population, and the mortality was 2.4 per 100,000 population in 201 [4]. Eastern Taiwan covers a land mass of 8144 km² (22.5% of Taiwan), but the population (554,400 in 2015) accounts for only 2.4% of the total population in Taiwan.

The target population for this study was MDR-TB patients enrolled for treatment from May 2007 to April 2017 in Eastern Taiwan. All newly diagnosed MDR-TB patients and MDR-TB patients reported previously but with persistent-positive cultures after January 2007 were enrolled and consented to participate in the TMTC program.

Regimen design

The initial MDR-TB regimens were designed by a panel of pulmonologists based on thorough reviews of patients' clinical characteristics and prior anti-TB treatment history and were given before DST results for second-line drugs became available in 3–8 weeks. The initial regimens included at least four anti-TB agents which were deemed effective. The regimens usually consisted of an injectable drug, a fluoroquinolone, and first-line drugs (ethambutol [EMB] and pyrazinamide) to which isolates were susceptible and other oral second-line drugs. Pyrazinamide was used unless DST results showed resistance. Subsequently, regimens were adjusted according to DST results for second-line drugs. Treatment lasted for 18–24 months, including at least 18 months after culture conversion. The actual duration of treatment was determined individually. The injectable drug was given for at least 6 months if feasible.

Multidrug-resistant tuberculosis case management

Seven mobile teams were organized for treatment support. Each team consisted of a nurse and a driver who also functioned as a bodyguard. Drugs were delivered to patients' homes or workplaces. The nurses provided directly observed therapy (DOT) twice a day from Mondays to Fridays and monitored adverse events and responses to treatment; treatment was self-administered by patients on Saturdays and Sundays.

Several measures were adopted to safeguard effective treatment support: (1) recruitment of highly motivated individuals committed to providing community-based DOT, (2) special training of public health nurses in providing psychosocial, cultural, and financial support, (3) provision of enablers and incentives to patients, which included transportation fees, free lunch boxes, varied stipends for daily expenses if patients were unable to work, social visits by clinicians, and holiday and birthday gifts, and (4) close monitoring and careful management of adverse drug effects. Support was consistently provided throughout the entire treatment period. Sputum smears and culture examinations were performed monthly during the treatment period. Chest radiographs (CXR) were performed every 3 months.

DST for first-line drugs (SM, isoniazid [INH], RMP, and EMB) was performed at the mycobacteriology laboratory

of Hualien Tzu Chi Hospital; confirmation of MDR-TB was systemically done by the national mycobacteriology reference laboratory at the Taiwan Centers for Disease Control (CDC). For confirmed MDR-TB cases, susceptibility testing for antituberculous drugs was performed by the national mycobacteriology reference laboratory at the Taiwan CDC using standardized phenotypic methods for kanamycin, capreomycin, amikacin, ofloxacin, levofloxacin, moxifloxacin, ethionamide, para-aminosalicylic acid (PAS), rifabutin, and pyrazinamide.

Patient data including age, gender, TB treatment history, sites of TB disease, human immunodeficiency virus (HIV) status, sputum smears, cultures and DST results, CXR findings, treatment regimens, outcomes, and comorbidities (such as diabetes mellitus, malignancy, end-stage renal disease, chronic liver disease, psychosis, stroke, and silicosis) were collected. The programmatic management of MDR-TB was entirely funded by the Taiwan CDC. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the institution. Informed written consent was waived because the study was a retrospective data analysis.

Definitions of outcomes

The six mutually exclusive treatment outcome categories recommended by the WHO (cure, treatment completion, transfer out, loss-to-follow-up, death, and treatment failure) were used in outcome assessment. Cure and treatment completion were classified as successful outcomes; death, loss-to-follow-up, failure, and transfer out were considered poor outcomes [5].

Patients who had 2 consecutive negative sputum cultures taken at least 30 days apart after enrollment were considered to have sputum culture conversions. The time to sputum culture conversion was defined as the interval between the date of enrollment for MDR-TB treatment and the date of collection of the first negative sputum culture in a series of two or more cultures taken at least 30 days apart.

Statistical analysis

Analyses were conducted using SAS statistic software, version 9.4 (SAS Institute Inc., Cary, NC, USA). Categorical data were analyzed with Chi-square test or Fisher's exact test. We conducted logistic regression to evaluate the odds ratios (ORs) and 95% confidence intervals (CIs). A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

A total of 178 patients with bacteriological confirmed pulmonary MDR-TB were identified. Of the 178 MDR-TB cases, 167 had treatment outcomes when the study was conducted and 11 were still receiving treatment. Among the 167 MDR-TB patients, 85 (50.9%) were new cases, 58 (34.7%) had been previously treated with first-line anti-TB drugs only, and 24 (14.4%) with second-line drugs; 122 (73.1%) were men. The mean age was 51.8 years (range 13–92) for men and 46.5 years (range 12–93) for women. The most common comorbidities were diabetes mellitus (42, 25.1%), cancer

(9, 5.4%), psychosis (7, 4.2%), and stroke (12, 7.2%). The mean body mass index was 22.0 kg/m².

Among these 167 patients, 113 (67.7%) were smear positive and 64 (38.3%) had cavitations on CXR; 147 patients were tested for HIV infection and none were HIV seropositive and 20 refused HIV testing. All 167 patients received a fluoroquinolone and 158 patients (94.6%) received an injectable agent.

Of the 167 patients, 120 (71.9%) were cured, 11 (6.5%) completed therapy (78.4% had successful treatment), 25 (15.0%) died, 9 (5.4%) had treatment failure, none were transferred out, and 2 (1.2%) were lost to follow-up. Surgery was performed on 8 (4.8%) of the 167 patients of whom 5 were cured, 2 died, and 1 had failed treatment. A total of 108 (64.7%) were admitted to the hospital, and the mean duration of hospitalization was 47.9 days (range 2–294 days).

Ten (6.0%) patients did not achieve sputum culture conversion, including 8 patients with failed treatment and 2 patients who died with positive sputum cultures. The mean conversion time was 46.7 days (range 0–574) in the 157 patients who had sputum conversion. Of the 167 patients, 68 (40.7%) had negative cultures at the onset of MDR-TB treatment. After treatment for 3 months, only 34 (20.4%) patients' sputum remained culture positive. After 6 months of treatment, only 19 (11.4%) patients had positive cultures. Of the 25 patients who died during treatment, only 2 patients (8.0%) had positive cultures at death and 10 (40.0%) patients died within 3 months after starting treatment.

At least one adverse drug reaction was reported in 154 (92.2%) patients. Most adverse drug events were minor. Two patients stopped treatment permanently, and adverse drug effects resulting in permanent withdrawal of one or more drugs in 62 (37.1%) patients. The five most common adverse drug events were nausea/vomiting (54.5%), arthralgia (47.3%), dizziness/vertigo (34.7%), hepatitis (27.5%), and hypothyroidism (10.2%).

In this study, we found 16 strains (9.6%) resistant to both INH and RMP but susceptible to all other tested drugs. One patient with extensively drug-resistant TB was identified and was cured after 23 months of treatment.

In addition to INH and RMP resistance, 128/153 (83.7%) were resistant to rifabutin, 78/167 (46.7%) to EMB, 71/167 (42.5%) to SM, 5/163 (3.1%) to kanamycin, 2/153 (1.3%) to capreomycin, 45/130 (34.6%) to ofloxacin, 26/79 (32.9%) to moxifloxacin, 24/92 (26.1%) to levofloxacin, 32/160 (20.0%) to ethionamide, and 19/163 (11.7%) to PAS [Figure 1].

In univariate analysis, age ($P < 0.01$) and previous treatment history ($P < 0.01$) were significantly associated with the outcome of treatment but not sex, body mass index, race, alcohol abuse, bacterial smear results, radiograph cavitations, and comorbidity [Table 1]. In multivariate analysis, older age (adjusted OR [aOR], 0.05; 95% CI, 0.01–0.26), positive sputum smear result (aOR, 0.25; 95% CI, 0.07–0.92), comorbidity with cancer (aOR, 0.14; 95% CI, 0.02–0.82), and

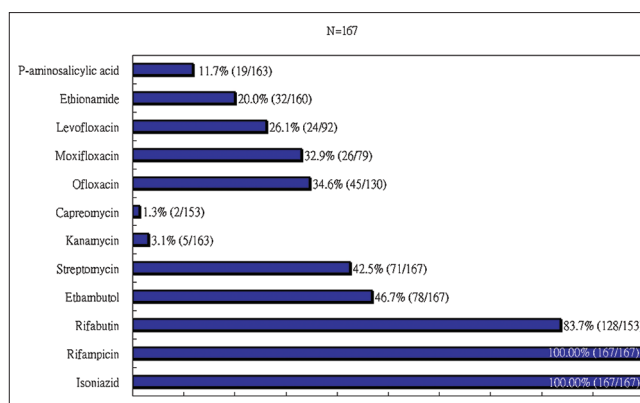


Figure 1: Proportions of multidrug-resistant tuberculosis patients with baseline resistance to first-line and second-line antituberculosis drugs in eastern Taiwan, 2007–2017

previous treatment with second-line drugs (aOR, 0.26; 95% CI, 0.07–0.93) were associated with a poor outcome.

DISCUSSION

The treatment success rate in MDR-TB patients in Eastern Taiwan was 78.4% in this study, which was much better than that in a group of 299 MDR-TB patients enrolled from 1992 to 1996 in northern Taiwan (51.2% treatment success, 9.4% death, 29.1% loss-to-follow-up, and 10.5% failure) [6]. The most striking difference between these two studies was that the proportion of loss-to-follow-up decreased substantially from 29.1% to 1.2%, resulting in the significant difference in the treatment success rates. DOTS and DOTS-Plus strategies were not implemented during that period (1992–1996) in Taiwan. Following implementation of the TMTC program in Eastern Taiwan in 2007, we observed a decreased default rate.

A recent systematic review of 33 studies of MDR-TB treatment outcomes by Orenstein *et al.* reported a successful outcome of only 62.0% [7]. The unsatisfactory results were mainly due to a high proportion of loss-to-follow-up, which is a serious global threat in the treatment and control of MDR-TB. The proportion of loss-to-follow-up exceeded 15% in many countries, including Korea (32.2%) [8], Taiwan (29.1%) [6], South Africa (21.0%) [9], Russia (20.0%) [10], Argentina (19.9%) [11], Peru (19.0%) [12], India (18.0%) [13], Nepal (17.0%) [14], Norway (17.0%) [15], and Italy (16.6%) [16].

An important factor associated with loss-to-follow-up is drug adverse reactions. These can be managed by early detection, timely treatment, close surveillance, and prompt management by a well-trained team consisting of community health workers, nurses, and physicians. High treatment costs may also be associated with loss-to-follow-up^[2] which could be addressed by public funding and/or private donations.

Teamwork and frequent nurse–patient interactions can help ensure adherence to treatment. Multidisciplinary approaches may ensure early identification and timely management of adverse drug events. Continuous psychosocial support was provided in our service to assist patients in

Table 1: Factors associated with outcomes of treatment (n=167)

Variables	Total (n)	Treatment success, n (%)	Poor outcome, n (%)	Crude OR (95% CI)	P	Adjust OR (95% CI)	P
Sex					0.7665		0.9022
Female	45	36 (80.0)	9 (20.0)	Reference		Reference	
Male	122	95 (77.9)	27 (22.1)	0.88 (0.38-2.05)		0.93 (0.31-2.80)	
Age					0.001		0.0003
<45	71	61 (85.9)	10 (14.1)	Reference		Reference	
45-65	61	51 (83.6)	10 (16.4)	0.84 (0.32-2.17)	0.7125	1.17 (0.34-4.06)	
>65	35	19 (54.3)	16 (45.7)	0.19 (0.08-0.50)	0.0007	0.05 (0.01-0.26)	
Aboriginal					0.4135		0.3838
No	51	38 (74.5)	13 (25.5)	Reference		Reference	
Yes	116	93 (80.2)	23 (19.8)	1.38 (0.64-3.01)		0.60 (0.19-1.90)	
Sputum smear result					0.2908		0.0369
M-	54	45 (83.3)	9 (16.7)	Reference		Reference	
M+	113	86 (76.1)	27 (23.9)	0.64 (0.28-1.47)		0.25 (0.07-0.92)	
Cavitation on CXR					0.217		0.6862
No	103	84 (81.6)	19 (18.4)	Reference		Reference	
Yes	64	47 (73.4)	17 (26.6)	0.63 (0.30-1.32)		0.78 (0.24-2.59)	
BMI					0.5364		0.8569
<18.5	28	21 (75.0)	7 (25.0)	Reference		Reference	
18.5-24	87	70 (80.5)	17 (19.5)	1.69 (0.64-4.50)	0.2928	1.43 (0.40-5.05)	
>24	52	40 (76.9)	12 (23.1)	1.24 (0.44-3.50)	0.6871	1.34 (0.34-5.22)	
Alcohol abuse					0.5934		0.5936
No	129	100 (77.5)	29 (22.5)	Reference		Reference	
Yes	38	31 (81.6)	7 (18.4)	1.28 (0.51-3.22)		0.71 (0.21-2.46)	
Diabetes mellitus					0.3999		0.1336
No	125	100 (80.0)	25 (20.0)	Reference		Reference	
Yes	42	31 (73.8)	11 (26.2)	0.70 (0.31-1.59)		0.42 (0.14-1.30)	
Cancer					0.1009		0.03
No	158	126 (79.7)	32 (20.3)	Reference		Reference	
Yes	9	4 (44.4)	5 (55.6)	0.32 (0.08-1.25)		0.14 (0.02-0.82)	
Stroke					0.0899		0.1817
No	155	124 (80.0)	31 (20.0)	Reference		Reference	
Yes	12	7 (58.3)	5 (41.7)	0.35 (0.10-1.18)		0.33 (0.06-1.69)	
Psychosis					0.6362		0.921
No	160	125 (78.1)	35 (21.9)	Reference		Reference	
Yes	7	6 (85.7)	1 (14.3)	1.68 (0.20-14.42)		0.88 (0.06-12.18)	
Fluoroquinolone resistance					0.0545		0.2326
No	107	89 (83.2)	18 (16.8)	Reference		Reference	
Yes	47	31 (66.0)	16 (34.0)	0.39 (0.18-0.86)	0.0198	0.49 (0.18-1.33)	
Unknown	13	11 (84.6)	2 (15.4)	1.11 (0.23-5.45)	0.8955	1.80 (0.28-11.82)	
Previous treatment history					0.0057		0.0006
New patient	85	67 (78.8)	18 (21.2)	Reference		Reference	
Previously treated with first line drugs only	58	51 (87.9)	7 (12.1)	1.96 (0.76-5.04)	0.1641	6.12 (1.64-22.87)	
Previously treated with second line drugs	24	13 (54.2)	11 (45.8)	0.32 (0.12-0.83)	0.0188	0.26 (0.07-0.93)	

CXR: Chest radiograph, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index

addressing both medical and nonmedical issues that may result in nonadherence. Building friendly relationships based on trust, compassion, and respect is the most important element in our treatment program. Cellular phones were provided to the patients to allow free and timely access to nurses for any medical, social, or financial problems. These measures could have been key factors in achieving the low proportion of loss-to-follow-up in our study. Adverse drug effects were promptly managed to relieve symptoms. Drugs suspected to

cause the adverse reactions were discontinued and replaced by an alternative drug after consultation with the physician.

The duration of hospitalization of MDR-TB patients decreased considerably. This reduced the costs of hospitalization, minimized disruption of social life, and also prevented nosocomial spread of resistant strains, an important consideration since many outbreaks of MDR-TB have been reported in hospitals [12,17,18].

When issues related to adherence are addressed, the main culprit for failing to achieve treatment success would be the lack of efficacious drugs. Two new drugs (bedaquiline and delamanid) were not used in this case series. Regimens including new drugs may reduce the risk of death and treatment failure, and treatment outcomes may further improve when these two new drugs become universally available [19,20].

CONCLUSIONS

This is an analysis of the treatment outcomes in 167 of 178 patients after adopting the DOTS-Plus program in treating MDR-TB patients in Eastern Taiwan. We had a low proportion of loss-to-follow-up, resulting in an increase in the treatment success rate to 78.4%. Measures to ensure adherence included the use of cellular phones to promote rapport between patients and nurses, prompt identification of adverse drug events for timely intervention, and psychosocial support and financial assistance to enhance adherence. This DOTS-Plus program can serve as an effective model for providing quality care to patients with MDR-TB. Other countries where the treatment success rate of programmatic management of drug-resistant TB remains unsatisfactory can adopt our approach, which might be helpful in global confrontation of the threat of MDR-TB.

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Conflicts of interest

There are no conflicts of interest.

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